

EDITORIAL COMMENT

Optimal Stent Expansion and Complete Neointimal Coverage

Does This Association Make Sense?*

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In this issue of *JACC: Cardiovascular Interventions*, Sera et al. (1) report that stent underexpansion (analyzed using intravascular ultrasound) is associated with incomplete neointimal coverage (determined by angiography) after sirolimus-eluting stent implantation; incomplete neointimal coverage is a pathologic risk factor for late stent thrombosis.

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For the same sized vessels, complete neointimal coverage was associated with a larger minimum stent area (MSA) when compared with incomplete coverage. Besides the methodological limitations typical for any small study, does this link make sense? The authors explain their findings by citing animal study histopathologic data from the bare-metal stent (BMS) era relating neointimal hyperplasia to vessel injury, especially to strut penetration into the media (2). They suggest that: 1) a larger MSA is inferential evidence of vessel injury; and 2) with BMS this is “bad” since it leads to more restenosis while in drug-eluting stents (DES) this is “good” since it increases completeness of stent strut tissue coverage.

We are not so sure. First, these histopathologic studies are in BMS, not in DES; to our knowledge, the stepwise relationship between an injury score and intimal hyperplasia has not been confirmed in DES. Second, these studies are mostly from nonatherosclerotic animal models. Third, in post-mortem human studies, only one-third of stents contact the media (3); moreover, stents do not penetrate the media at the site of maximum plaque burden, typically the site of the MSA. Fourth, even in BMS (with the exception of the Hoffmann et al. study [4]), there is no consistent evidence that a larger MSA is associated with a greater

neointimal response. Fifth, the relationship between injury and intimal hyperplasia in BMS is focal, on a slice-by-slice or even strut-by-strut basis. Why should stent underexpansion at the MSA site contribute to incomplete strut coverage at other sites or throughout the stent?

Instead, we believe that other explanations are worth exploring. For example, atherosclerosis, neointimal hyperplasia, and stent thrombosis predominantly develop at sites of low wall shear stress that is inversely proportional to the cube of the radius (5). Sukavaneshvar et al. (6) have demonstrated that platelet-dependent thrombosis is promoted by increasing radial transport of blood components and low wall shear stress. Low shear stress might be a risk factor for stent thrombosis for as long as the mechanical cause exists even though most reports related early stent thrombosis to stent underexpansion (7,8). Thus, in BMS stent underexpansion (and low shear stress) may result in “incomplete” endothelialization that may accelerate neointimal growth (5,9). However, in DES the eluted drug suppresses neointimal growth and re-endothelialization so that underexpansion may result in thrombus formation in areas of low wall shear stress (10,11). While the primary aim of DES is preventing vascular smooth muscle cell proliferation and migration, the eluted drugs also impair re-endothelialization leading to delayed arterial healing, induced tissue factor expression, and a prothrombotic environment (12,13).

Angioscopy and optical coherence tomography are the best clinical tools to evaluate tissue stent strut coverage (14–17), but they do not evaluate the function of the endothelium or even the existence of re-endothelialization; re-endothelialization is below the current resolution of these techniques. In addition, although 1 post-mortem study has shown that the most powerful morphologic predictor of stent thrombosis is tissue coverage (18), there is no strong evidence that clinically detected incomplete stent strut coverage leads to stent thrombosis. Many DES with incomplete strut stent coverage do not thrombose (15,17,19) although subclinical stent thrombus formation may be under-recognized (20).

Mechanical factors such as stent underexpansion are more important in early thrombosis, whereas patient factors such as cessation of antiplatelet agents are more important in late/very late DES thrombosis (11). Studies have also shown that inflow/outflow disease or a larger residual reference segment plaque burden is a risk factor for stent thrombosis (6–8). To that end, in the study by Sera et al. (1), stents with incomplete neointima coverage had a smaller distal reference lumen area and a tendency for a greater distal reference plaque burden.

There are many limitations to this study including the lack of baseline pre-DES imaging. However, most importantly, the authors only report 28 stented segments in 15 patients. Even in this very small study, most patients had

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multiple stented segments. Did individual stented segments in the same patient behave independently or were they influenced by patient-related factors; if there were 2 stents in 1 patient, were they equally expanded and/or did they have similar neointimal coverage? For example, there was an interesting trend relating diabetes to neointimal coverage that was never explored. Another limitation is the assessment of neointimal coverage by angiography (14,15). Using angiography, complete circumferential view of the entire stent length may be prohibited by vascular tortuosity (15).

Furthermore, unlike animal models relating local neointimal tissue versus focal vessel injury on a slice-by-slice or strut-by-strut basis and pathologic studies showing heterogeneity of DES neointima, angiographic classification of neointimal coverage is global and not regional while stent expansion is evaluated at 1 slice—the MSA site. Especially when assessing the relationship between stent expansion, neointimal hyperplasia, and thrombus formation, the intrastent “regional” environment (low shear stress) and blood flow is more complicated and dependent on 3-dimensional stent as well as inflow/outflow geometry (6).

The current study combined angiographic and intravascular ultrasound findings. In the future optical coherence tomography, which can assess both MSA and strut-by-strut neointimal coverage over the entire length of the stent (16,17) as well as other potentially important findings such as stent-vessel wall malapposition and atherosclerotic and neointimal plaque composition, may be preferred for such studies.

Nevertheless, Sera et al. (1) provide a novel explanation for the relationship between stent underexpansion and stent thrombosis—that stent underexpansion limits stent strut neointimal coverage and, therefore, could promote stent thrombosis. Does their data and explanation make sense? Perhaps. Perhaps not. However, the authors provide another compelling reason to optimize DES expansion and not just settle for “good enough.”

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